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EMA Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

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I. Scope and legal basis of the reflection paper

II. Laboratory management and SOPs

III. Trial conduct

IV. Examples of findings from GCP inspections

Reflection paper for laboratories that perform the analysis or evaluation of clinical trial samples

- Public consultation September 2010
- Deadline for comments February 2011
- Adopted by the GCP Inspectors Working Group February 2012

Commission Directive 2001/20/EC

- Article 1, 2:
  Good clinical practice is a set of internationally recognized ethical and scientific **quality requirements** which must be observed for the **design**, **conduct**, **recording** and **reporting** of **clinical trials** that involve the participation of human subjects. Compliance with this good practice provides assurance that the **rights**, **safety** and **well-being** of **trial subjects** are **protected**, and that the **results** of the **clinical trials** are **credible**.

Commission Directive 2005/28/EC

Chapter 2
Good clinical practice for the design, conduct, recording and reporting of clinical trials

Section 1 Article 2, 4:

The **necessary procedures** to **secure** the **quality** of **every aspect** of the **trials** shall be **complied** with.

Note for guidance on Good Clinical Practice

- 5.1.1 The sponsor is responsible for **implementing** and **maintaining quality assurance** and **quality control systems** with **written SOPs** to **ensure** that **trials** are **conducted** and **data** are **generated**, **documented** (**recorded**), and **reported** in **compliance** with the **protocol**, GCP, and the **applicable regulatory requirement(s)**.
- 5.2.1 A sponsor may transfer any or all of the sponsor's trial-related duties and functions to a CRO… The CRO should **implement quality assurance** and **quality control**.

Purpose of the reflection paper

- Provide **information** that will help to **develop** and **maintain quality systems** in order to **comply** with **relevant regulation** and guidance
- Complements existing quality systems
- **Applicable** to all **laboratories** that generate data submitted to regulatory authorities as part of a **clinical trial application** or **marketing authorisation application**

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Laboratory management

- ✓ Quality assurance and quality control process
- ✓ Sufficient resources: educated, experienced and trained personnel
- ✓ Job descriptions: roles and responsibilities defined and documented
- ✓ Communication lines established
- ✓ Standard Operation Procedure (SOP) system for key activities
- ✓ Archiving of documents

Facilities and Equipment

- ✓ Facilities of suitable size, construction and location
- ✓ Adequate degree of separation to assure a proper conduct of the work
- ✓ Maintain adequate storage conditions for samples / reagents
- ✓ Maintenance of equipment
- ✓ Develop / validate / maintain computerized systems

SOPs and facility policies

- Written procedures should be in place including processes for
  - ✓ Preparation
  - ✓ Review
  - ✓ Authorisation
  - ✓ Release
  - ✓ Distribution
  - ✓ Periodic review / revision
  - ✓ Training

  of a SOP / document
- Work instructions / SOPs for key activities

Examples of key activities – “Quality”

- Quality assurance and quality control functions
- Training
- Reporting of data / results
- Handling and reporting issues such as patient safety issues or un-blinding
- Deviation management and reporting
- Retention of data and archiving

Examples of key activities – “Operation”

- Method validation
- Equipment maintenance
- Computerized system validation
- Receipt / storage / processing of samples / reference materials
- Performance and reporting of the analysis and evaluation of clinical trial samples

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Before the trial starts

- ✓ Written contract / agreement between sponsor & lab
- ✓ Key document: **clinical trial protocol**
- ✓ Work instructions / SOP for all tasks in place
- ✓ Consistency sustained between all documents: contract / protocol / work instructions
- ✓ Staff trained in all relevant tasks
- ✓ Equipment and tests qualified / validated

Conduct of the trial

- ✓ Work done by the lab covered by the protocol?
- ✓ Protocol amendments relevant for the laboratory?
- ✓ Documentation of tasks performed
  accurate, complete, legible and in a timely manner?
- ✓ Documentation of deviations from the protocol,
  impact assessment?
- ✓ Timely reporting to the sponsor by established
  communication lines?

From the sample to the data

- ✓ Appropriate transport / storage conditions defined, temperature monitoring required
- ✓ Integrity check at sample receipt, cross-check samples and requisition form
- ✓ Record of sample receipt: “booking in“
- ✓ Traceability and documentation on sample handling, e.g. preparation of aliquots, freeze-thaw-cyles
- ✓ Analysis of the sample
- ✓ Documentation of results

Patients safety and rights

- ✓ Reporting line defined for abnormal results / expedited communication?
- ✓ Mechanism in place to receive information about withdrawal of participants consent and to implement actions?
- ✓ Mechanism in place to notify inappropriate labelling, e.g. trial participant's identification on the sample?
- ✓ Mechanism in place to ensure the trial participants' safety and rights are not compromised?

Quality assurance activities

- ✓ Effective / independent quality assurance unit?
- ✓ Review of the quality system
- ✓ Audit of critical analytical phases
- ✓ Audit of technical procedures used to perform / evaluate clinical trial samples
- ✓ Documentation audit
- ✓ Laboratory audit to ensure it is **fit for purpose**

Quality control activities

“Quality Control” means a formal process for the systematic checking of processes and data to ensure accuracy, e.g.

- ✓ In-process controls
- ✓ Document checks on consistency
- ✓ Documentation checks on accuracy / completeness
- ✓ Data accuracy check prior to approval

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Examples of findings from GCP-inspections

- Samples received beyond the point of stability, no communication / corrective action to the issue
- Specification for storage time / conditions for samples not defined
- Acceptance criteria for critical reagents not defined
- No specifications for repeat analysis

Examples of findings from GCP-inspections

- Assay / equipment used without qualification / calibration / validation
- Wrong buffer used for reconstitution
- Patient identity revealed on sample label
- No quality assurance / quality control system in place
- No evidence on GCP-training, documentation on training of staff not available

Good clinical practice
is key for the
protection of **study participants'**
safety and **rights**
and for the
generation of **sound data**

Thank you for your attention

Any questions?

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Grading of GCP-Inspection Findings

Critical

Conditions, practices or processes that adversely affect the rights, safety or well-being of the subjects and / or the quality and integrity of data. Critical observations are considered totally unacceptable. Possible Consequences: Rejection of data and / or legal action required. Observation classified as critical may include a pattern of deviations classified as major, bad quality of the data and / or absence of source documents. Manipulation and intentional misinterpretation of data belongs to this group.

Major

Conditions, practices or processes that might adversely affect the rights, safety or well-being of the subjects and / or the quality and integrity of data. Major observations are serious deficiencies and are direct violations of GCP principles. Possible Consequences: Data may be rejected and / or legal action required. Observation classified as major may include a pattern of deviations and / or numerous minor observations.

Minor

Conditions, practices or processes that would not be expected to adversely affect the rights, safety or well-being of the subjects and / or the quality and integrity of data. Observations classified as minor indicate the need for improvement of conditions, practices and processes. Many minor observations might indicate a bad quality and the sum might be equal to a major finding with its consequences.

- http://www.emea.europa.eu/Inspections/docs/gcp/INS-GCP-4.pdf